09/782,378

03CC

04420/03/29/2001

PATENT

Attorney Docket No. **STONYB-04970**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Patrick Hearing *et al.*
Serial No.: Group No.:
Filed: Examiner:
Entitled: **HYBRID ADENOVIRUS/ADENO-ASSOCIATED VIRUS VECTORS AND METHODS OF USE THEREOF**

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231

Dated: April 4, 2001 By: Marilyn Moy
Marilyn Moy

Sir or Madam:

Enclosed please find an Information Disclosure Statement and Form PTO-1449, including copies of the references contained thereon, for filing in the U.S. Patent and Trademark Office.

The Commissioner is hereby authorized to charge any additional fee or credit overpayment to our Deposit Account No. **08-1290**. **An originally executed duplicate of this transmittal is enclosed for this purpose.**

Dated: April 4, 2001

Kamrin T. MacKnight
Registration No. 38,230

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104
415/705-8410

PATENT
Attorney Docket No. **STONYB-04970**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Patrick Hearing *et al.*
Serial No.: 09/782,378 Group No.: Not yet assigned
Filed: 02/12/01 Examiner: Not yet assigned
Entitled: **HYBRID ADENOVIRUS/ADENO-ASSOCIATED VIRUS VECTORS AND METHODS OF USE THEREOF**

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231 on **April 4, 2001**.

By: Marilyn Moy
Marilyn Moy

Sir or Madam:

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

The following patents are referred to in the body of the specification:

- U.S. Patent No. 6,040,174 issued 3/21/00 to Imler *et al.*;
- U.S. Patent No. 5,872,005 issued 2/16/99 to Wang *et al.*;
- U.S. Patent No. 5,837,484 issued 11/17/98 to Trempe *et al.*;
- U.S. Patent No. 5,589,377 issued 12/31/96 to Lebkowski *et al.*;
- U.S. Patent No. 5,789,390 issued 8/4/98 to Descamps *et al.*;
- U.S. Patent No. 5,691,176 issued 11/25/97 to Lebkowski *et al.*;
- U.S. Patent No. 4,683,195 issued 7/28/87 to Mullis *et al.*;
- U.S. Patent No. 4,683,202 issued 7/28/87 to Mullis;
- WO 91/18088 published 11/28/91;
- WO 90/09441 published 8/23/90;

- WO 88/10311 published 12/29/88;
- WO 91/11525 published 8/8/91; and
- EP 185 573 published 5/20/92.

The following printed publications are referred to in the body of the specification:

- Benihoud *et al.* (1999) "Adenovirus vectors for gene delivery," Curr. Opin. Biotechnol. 10:440-7;
- Brenner (1999) "Gene Transfer by Adenovectors," Blood 94:3965-7;
- Kochanek (1999) "High-Capacity Adenoviral Vectors for Gene Transfer and Somatic Gene Therapy," Hum. Gene. Ther. 10:2451-9;
- Wold (1999) "Immune responses to adenoviruses: viral evasion mechanisms and their implications for the clinic," Human Press, Totowa, NJ;
- Tripathy *et al.* (1996) "Immune responses to transgene-encoded proteins limit the stability of gene expression after injection of replication-defective adenovirus vectors," Nat. Med. 2:545-50;
- Yang *et al.* (1996) "Role of Viral Antigens in Destructive Cellular Immune Responses to Adenovirus Vector-Transduced Cells in Mouse Lung," J. Virol. 70:7209-12;
- Thrasher et al. (1995) "Generation of recombinant adeno-associated virus (rAAV) from an adenoviral vector and functional reconstitution of the NADPH-oxidase," Gene Ther. 2:481-485;
- Fisher *et al.* (1996) "A Novel Adenovirus-Adeno-Associated Virus Hybrid Vector That Displays Efficient Rescue and Delivery of the AAV Genome," Human Gene Ther. 7:2079-2087;
- Lieber *et al.* (1999) "Integrating Adenovirus-Adeno-Associated Virus Vectors Devoid of All Viral Genes," J. Virol. 73:9314-9324;
- Liu *et al.* (1999) "Production of recombinant adeno-associated virus vectors using a packaging cell line and a hybrid recombinant adenovirus," Gene Ther. 6:293-299;
- Berns *et al.* (1995) "Adenovirus and Adeno-Associated Virus as Vectors for Gene Therapy," Ann. NY Acad. Sci. 772:95-104;

- Muzyczka (1992) "Use of Adeno-Associated Virus as a General Transduction Vector for Mammalian Cells," Curr. Top. Microbiol. Immunol. 158:97-129;
- Rolling and Samulski (1995) Mol. Biotechnol. 3:9-15[1];
- Bett *et al.* (1993) "Packaging Capacity and Stability of Human Adenovirus Type 5 Vectors," J. Virol. 67:5911-21;
- Parks and Graham (1997) "A Helper-Dependent System for Adenovirus Vector Production Helps Define a Lower Limit for Efficient DNA Packaging," J. Virol. 71:3293-8;
- Akli *et al.* (1993) "Transfer of a foreign gene into the brain using adenovirus vectors," Nature Genetics 3:224;
- Stratford-Perricaudet *et al.* (1990) "Evaluation of the Transfer and Expression in Mice of an Enzyme-Encoding Gene Using a Human Adenovirus Vector," Human Gene Ther. 1:241;
- Levrero *et al.* (1991) "Defective and nondefective adenovirus vectors for expressing foreign genes in vitro and in vivo," Gene 101:195;
- Le Gal la Salle *et al.* (1993) "An Adenovirus Vector for Gene Transfer into Neurons and Glia in the Brain," Science 259:988;
- Roemer and Friedmann (1992) "Concepts and strategies for human gene therapy," Eur. J. Biochem. 208:211;
- Dobson *et al.* (1990) "A Latent, Nonpathogenic HSV-1-Derived Vector Stably Expresses β-Galactosidase in Mouse Neurons," Neuron 5:353;
- Chiocca *et al.* (1990) "Transfer and Expression of the *lac*Z Gene in Rat Brain Neurons Mediated by Herpes Simplex Virus Mutants," New Biol. 2:739;
- Miyanohara *et al.* (1992) "Direct Gene Transfer to the Liver with Herpes Simplex Virus Type 1 Vectors," Transient Production of Physiologically Relevant Levels of Circulating Factor IX," New Biol. 4:238;
- Xiao et al. (1997) "A Novel 165-Base-Pair Terminal Repeat Sequence Is the Sole *cis* Requirement for the Adeno-Associated Virus Life Cycle," J. Virol. 71:941-948;

---

[1] Applicant is unable to obtain a copy of this reference, and will provide the Examiner with a copy as soon as one is available to Applicant.

- Ryan et al. (1996) "Sequence Requirements for Binding of Rep68 to the Adeno-Associated Virus Terminal Repeats," J. Virol. 70:1542-1553;
- Imler *et al.* (1996) "Novel complementation cell lines derived from human lung carcinoma A549 cells support the growth of E-1 deleted adenovirus vectors," Gene Ther. 3:75-84;
- Fallaux *et al.* (1998) "New Helper Cells and Matched Early Region 1-Deleted Adenovirus Vectors Prevent Generation of Replication-Competent Adenoviruses," Human Gene Ther. 9:1909-1917;
- Fallaux *et al.* (1996) "Characterization of 911: A New Helper Cell Line for the Titration and Propagation of Early Region 1-Deleted Adenoviral Vectors," Human Gene Ther. 7:215-222;
- Weinberg *et al.* (1983) "A cell line that supports the growth of a defective early region 4 deletion mutant of human adenovirus type 2," Proc. Natl. Acad. Sci. USA 80:5383-5386;
- Brough *et al.* (1996) "A Gene Transfer Vector-Cell Line System for Complete Functional Complementation of Adenovirus Early Regions E1 and E4," J. Virol. 70:6497-501;
- Hearing *et al.* (1987) "Identification of a Repeated Sequence Element Required for Efficient Encapsidation of the Adenovirus Type 5 Chromosome," J. Virol. 61:2555-8;
- Zolotukhin *et al.* (1996) "A 'Humanized' Green Fluorescent Protein cDNA Adapted for High-Level Expression in Mammalian Cells," J. Virol. 70:4646-54;
- Stow (1981) "Cloning of a DNA Fragment from the Left-Hand Terminus of the Adenovirus Type 2 Genome and Its Use in Site-Directed Mutagenesis," J. Virol. 37:171-180;
- Graham *et al.* (1977) "Characteristics of a Human Cell Line Transformed by DNA from Human Adenovirus Type 5," J. Gen. Virol. 36:59-74;
- Thimmappaya et al. (1982) "Adenovirus VAI RNA Is Required for Efficient Translation of Viral mRNAs at Late Times after Infection," Cell, Dec. 31 (3 Pt 2): 543-551;

- Tollefson et al. (1996) "The Adenovirus Death Protein (E3-11.6K) Is Required at Very Late Stages of Infection for Efficient Cell Lysis and Release of Adenovirus from Infected Cells," J. Virol. 70(4):2296-2306;
- Steinwaerder *et al.* (1999) "Generation of Adenovirus Vectors Devoid of All Viral Genes by Recombination between Inverted Repeats," J. Virol. 73:9303-13;
- Clark *et al.* (1996) "A stable cell line carrying adenovirus-inducible rep and cap genes allows for infectivity titration of adeno-associated virus vectors," Gene Ther. 3:1124-32;
- Hirt (1967) "Selective Extraction of Polyoma DNA from Infected Mouse Cell Cultures," J. Mol. Biol. 26:365-9;
- Nevins (1981) "Mechanism of Activation of Early Viral Transcription by the Adenovirus E1A Gene Product," Cell 26:213-20; and
- Sandalon *et al.* (1997) "*In Vitro* Assembly of SV40 Virions and Pseudovirions: Vector Development for Gene Therapy," Hum. Gene Ther. 8:843-9.

Applicant has become aware of the following printed publications which may be material to the examination of this application:

- U.S. Patent No. 5,877,011 issued 3/2/99 to Armentano *et al.* Armentano *et al.* discloses chimeric adenoviral vectors which contain (1) the nucleotide sequence of Ad2 or Ad5 in which one or more E4 reading frames is deleted, (2) a transgene operably linked to a eukaryotic promoter, and (3) a replacement of the nucleotide sequence encoding Ad2 or Ad5 fiber protein with the nucleotide sequence encoding Ad 17 fiber protein. However, Armentano *et al.* does not disclose a recombinant vector, comprising in operable combination: 1) a nucleotide sequence of interest having a 5' end and a 3' end; 2) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; 3) adenovirus packaging sequence linked to one of the inverted terminal repeats; and 4) an adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence, and

either (a) lacks one or more adenovirus early gene region selected from E1, E2, E3, and E4 gene region, or (b) contains a nucleotide sequence of interest which comprises the adeno-associated virus rep gene region;

- U.S. Patent No. 5,891,690 issued 4/6/99 to Massie. Massie discloses an adenovirus E1-complementing cell line designated BMAdE1-220-8 (ATCC No. CRL-12407) which reduces the presence of replication competent adenovirus (RCA) and which is disclosed to be useful for the production of infectious E1-deleted adenoviral particles. Massie also discloses a recombinant vector (pHβE1AEIB) for transfecting eukaryotic cell lines to construct adenovirus E-1 complementing cell lines. The vector contains as a complementing element the human Ad5 coding region spanning nucleotides 532 to 3525 (GenBank M73260) (which consists of the E1A gene, the E1B promoter, and the E1B gene), and lacks the packaging and Ori sequences (the 5' ITR: 0-350). Expression of E1A is by the constitutive human β-actin promoter. Nonetheless, Massie does not disclose a recombinant vector, comprising in operable combination: 1) a nucleotide sequence of interest having a 5' end and a 3' end; 2) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; 3) adenovirus packaging sequence linked to one of the inverted terminal repeats; and 4) an adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence, and either (a) lacks one or more adenovirus early gene region selected from E1, E2, E3, and E4 gene region, or (b) contains a nucleotide sequence of interest which comprises the adeno-associated virus rep gene region;
- WO 99/53085 published 10/21/99 to inventors Hearing *et al.* This document discloses adenovirus vectors which contain one or more copies of a minimum packaging sequence, and optionally contain one or more repressor binding sites for the COUP-TF and *lac* repressors. This document also discloses a cellular complex, called the P complex, which functions in viral packaging and virus production. However, this document does not disclose a recombinant vector,

comprising in operable combination: 1) a nucleotide sequence of interest having a 5' end and a 3' end; 2) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; 3) adenovirus packaging sequence linked to one of the inverted terminal repeats; and 4) an adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence, and either (a) lacks one or more adenovirus early gene region selected from E1, E2, E3, and E4 gene region, or (b) contains a nucleotide sequence of interest which comprises the adeno-associated virus rep gene region;

- Gnatenko *et al.* (1999) "An Adenovirus/Adeno-associated Hybrid Virus Generates a Mini-Adenovirus Devoid of all Viral Genes," Blood (supplement) 94:181a, Abstract No. 788. This abstract discloses generation of two Ad/AAV hybrid viruses into E1a/E1b-deleted or E1a/E1b/E3 deleted Ad5 genomes and use of the vectors for high-level transgene expression in host cells. Gnatenko *et al.* also discloses the generation of mini-adenovirus (mAd) in either monomeric or dimeric forms, and that these mAds retained AAV terminal repeats (TR) and duplicated flanking Ad packaging sequences (Ψ). Purified mAd/GFP-Neo transduced Hela, COS-1 and HepG2 cells. However, the vectors of Gnatenko *et al.* do not comprise an adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest. Gnatenko *et al.*'s vectors are not disclosed to comprise the adeno-associated virus rep gene region;
- Molin *et al.* (1998) "Two Novel Adenovirus Vector Systems Permitting Regulated Protein Expression in Gene Transfer Experiments," J. Virol. 72:8358-8361. Molin *et al.* discloses two adenovirus vector systems. The first system is referred to as the Tet-ON system and it consists of the reverse tetracycline (Tet) repressor protein fused to the herpes simplex virus (HSV) VP16 transcriptional activation domain (rtTA) cloned behind the constitutively active cytomegalovirus (CMV) promoter and inserted into an adenovirus type 5 (Ad5) *dl*309 vector (generating virus AdCMVrtTA). The chloramphenicol

acetyltransferase (CAT) reporter gene was cloned behind a Tet enhancer consisting of seven tandem Tet operator DNA binding sites fused to a minimal adenovirus major late promoter/tripartite leader construct (virus AdTetTripCAT). Transcription of the CAT reporter gene is activated by the addition of doxycycline (DOX) to the culture medium. The second system is the progesterone antagonist-induced gene expression system which is referred to as the Prog system, and which contains a transactivator protein consisting of the ligand binding domain of hPRB891 fused to the Gal4 DNA binding domain and the HSV VP16 transactivator domain which was cloned behind a CMV promoter and inserted into an Ad5 *dl*309 vector (generating virus AdCMVProg). The CAT reporter gene was cloned behind a Gal4 enhancer consisting of five Gal4 DNA binding sites fused to a minimal major late promoter/tripartite leader construct (virus AdG5TripCAT). Transcription of the CAT reporter gene is activated by the addition of RU 486 to the culture medium. However, the vectors of Molin *et al.* do not comprise an adeno-associated virus terminal repeat sequence operably linked to the 3' end of a nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence. The vectors of Molin *et al.* also do not comprise the adeno-associated virus rep gene region;

- Recchia *et al.* (1999) "Site-specific integration mediated by a hybrid adenovirus/adeno-associated virus vector," Proc. Natl. Acad. Sci. USA 96:2615-2620. Recchia *et al.* discloses helper-dependent (HD) adenoviral vectors. Plasmid pRP1030 contains sequences corresponding to the left end (base pair 3-466) and to the right end (base pairs 35,464-35,924) of Ad5 genome including ITRs and packaging signal. All other Ad5 genomic sequences were deleted and substituted with a mouse cytomegalovirus immediate early promoter cassette. Plasmid HDFB1 contains an AAV-ITR-flanked cassette consisting of the green fluorescent protein (GFP) and hygromicin B resistance genes flanked by AAV-ITR sequences. The AAV-ITR-flanked cassette is ligated to Ad5 Ψ and the resulting sequence is flanked by Ad5 ITRs. Unlike the claimed vectors, the vectors of Recchia *et al.* do not comprise an adeno-associated virus terminal

repeat sequence operably linked to the 3' end of a nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence; and

- Sandalon *et al.* (2000) "AAV Rep Protein Enhances the Generation of a Recombinant Mini-Adenovirus Utilizing an Ad/AAV Hybrid Virus," J. Virol. 74:10381-9. Sandalon *et al.* is not prior art since the attached stamp from the University of California at San Francisco Library shows a receipt date of November 15, 2000, which is not prior to the priority filing date (October 2, 2000) of the provisional application Serial No. 60/237,747.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: April 4, 2001

Kamrin T. MacKnight
Registration No.38,230

Please direct all communication to:

Peter G. Carroll
Registration No.
MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104
415/705-8410